REMARKS

Claims 1-75 are currently pending in this application. Claims 18, 33-51, 58, 60-72, 74, and 75 have been canceled as directed to non-elected subject matter, without admission and without prejudice to Applicants right to pursue the subject matter of those canceled claims in either this or other (*e.g.*, related continuing or divisional) patent applications.

The specification has been amended at page 16, line 4, page 18, line 28, and at page 20, lines 12 and 21 to recite "rMal d 1 (2620)" instead of "Mal d 1 (2620)." Support for these amendments can be found at page 20, line 22 and original Figure 26. The specification has also been amended at page 30, line 12; page 31, lines 15 and 30; page 49, line 11; page 61, line 10; and page 63, line 26, to replace "Mal d 1 (2620)" with "rMal d 1 (2620)." Support for these amendments can be found in the Description of the Drawings, for example, at page 14, lines 13-14, 18-19, and 22-31.

Claim 3 has been amended to recite "10,000" instead of "10.000" in order to conform to U.S. numbering standards, as requested by the Examiner.

Claim 30 has been amended to delete the repetition of mutations K32X, E59X, and E95X, as requested by the Examiner. Additionally, repetition of the secondary mutation K122X has been deleted.

Claims 5, 6, 8, 11, 14, 54, and 57 have been amended to delete the "preferable" ranges and to recite only a single range limitation. New claims 76-92 have been added to claim the deleted range limitations. Support for claims these new claims can be found in claims 5-6, 8, 11, 14, 54, and 57, as originally filed with this application.

Claims 26 and 27 have been amended to recite the specific SEQ ID NOs and to delete references to specific mutations. Support for this amendment can be found at page 31, lines 5-31.

Claim 19 has been amended to incorporate the limitations of canceled claim 18. Support for this amendment can be found in original claim 18.

No new matter has been introduced in these amendments. Upon entry of these amendments. Claims 1-17, 19-32, 52-57, 59, and 73 will be pending. Entry and consideration of these amendments is respectfully requested.

Election/Restriction

Claims 18, 33-51, 58, 60-72, 74, and 75 are directed to subject matter that was not elected in Applicants' response to the Restriction Requirement for this application. Accordingly, claims 18, 33-51, 58, 60-72, 74, and 75 have been canceled in this amendment. However, the cancellation of these claims is made without admission and without prejudice to Applicants' rights to traverse the Requirement for Restriction and/or pursue the subject matter of the non-elected claims in either this or other (*e.g.*, related continuation or divisional) patent applications.

Objection to the Drawings

The Examiner has objected to Figure 26 specifically, and the remaining Figures generally, arguing that "rMal d 1 (2620)" should be labeled as "Mal d 1." Applicants respectfully note that the correct notation should be "rMal d 1 (2620)," as recited in the description of Figure 26 at page 20, line 22. Accordingly, the description of Figure 26 in the specification has been amended at page 20, lines 12 and 21 to recite "rMal d 1 (2620)" instead of "Mal d 1 (2620)." Support for these amendments can be found at page 20, line 22 and original Figure 26. Additionally, the description for Figure 21 has also been amended at page 18, line 28, and Figures 3B and 21 have been amended to recite "rMal d 1 (2620)" instead of "Mal d 1 (2620)." Support for these amendments can be found at page 20, line 22 and original Figure 26. Replacement sheets for Figures 3B and 21 are submitted herewith. Accordingly, Applicants submit that the Examiner's objection to the drawings has been obviated, and respectfully request that the objection be withdrawn.

Objection to the Specification

The Examiner has objected to the specification for various typographical errors, in addition to the interchangeable use of the terms "Mal d 1" and "rMal d 1." Applicants respectfully point out that the typographical errors identified by the Examiner have been corrected. Furthermore, the specification has been amended to replace "Mal d 1" with "rMal d 1" where appropriate. Support for these amendments can be found, for example, at page 14, lines 13-15. Accordingly, Applicants submit that the Examiner's objection to the specification has been obviated, and respectfully request that the objection be withdrawn.

Objections to the Claims

The Examiner has objected to claim 3 for reciting the term "10.000," and requests that the claim be amended to comply with the U.S. numbering system. Accordingly, Claim 3 has been amended so that it now recites "10,000." Applicants submit that the Examiner's objection has been obviated, and respectfully request that the objection be withdrawn.

The Examiner has also objected to claim 30 for repeating the secondary mutations K32X, E59X, and E95X. Applicants would like to point out that claim 30 has been amended to delete the repetition of secondary mutations K32X, E59X, and E95X. Additionally, repetition of secondary mutation K122X has also been deleted. Accordingly, Applicants submit that the Examiner's objection has been obviated, and respectfully request that the objection be withdrawn.

The Examiner has objected to claim 19 for being dependent upon a rejected base claim, but states that the claim would be allowable if rewritten in independent form including all of the limitations of the base claim, *e.g.*, claim 18. Accordingly, Applicants have amended claim 19 to incorporate the limitations of claim 18, and respectfully submit that the objection be withdrawn.

The Examiner has objected to claims 2-4, 7, 12-13, 16-17, and 29 for being dependent upon a rejected base claim. As explained below, Applicants submit that the rejections of these claims have now been obviated. Applicants respectfully decline to amend these claims at this time, other than to address typographical errors.

The Rejections Under the Second Paragraph of 35 U.S.C. § 112 Should Be Withdrawn

Claims 1, 5-6, 8, 11-12, 14, 25-28, 30-32, 53-54, and 57 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Office Action indicates that claim 1 is indefinite because the term "protective," which is recited in that claim, is merely the "opinion of the Applicants," and, as such, is unclear. In response, Applicants respectfully point out that the term "protective immune response" (the complete term recited in pending claim 1) is particularly defined in this application. *See*, in particular, in the application as originally filed at page 43, lines 1-7. This definition makes it clear that the term, as used in this application, specifically refers to responses resulting in the production of mediator substances, such as cytokines and antibodies, that is well known to occur upon the stimulation of leukocytes (including T and B lymphocytes). Applicants therefore submit that the term is fully definite within the context of the application.

The Office Action states that claim 5 is unclear due to the lack of a specific sequence reference in that claim. However, claim 5 clearly specifies that the protein variant recited in independent claim 1 should comprise a specific number of mutations. Apart from complying with the requirement set forth in claim 1, there is no requirement that these be mutations of any particular amino acid residues or that they be in any particular sequence. Applicants therefore respectfully submit that the claim is fully definite and that no sequence is required.

Claims 6 and 53 have also been rejected as indefinite for failing to recite a specific sequence reference. Specifically, the Examiner argues that the homology levels recited in these claims cannot be determined without reference to a specific sequence. In response, Applicants respectfully point out that the level of homology recited in these claims is between a "scaffold protein," as recited in claim 1, and the "naturally occurring allergen" from which it is derived. The sequence of a large number of naturally occurring allergens are already known in the art, and can be used to design scaffold proteins in accordance with the claimed invention. Indeed, such sequences are described in detail in the application as filed, *e.g.*, at page 29, line 25 to page 30, line 10, and page 33, lines 5-28. The claimed invention can be practiced using any of these various "natural

allergen" sequences and scaffold proteins derived therefrom. These claims are therefore fully definite without limiting the invention to any specific sequence.

Claims 5-6, 8, 11, 14, 54, and 57 have been rejected as indefinite due to the recitation of "preferable" ranges in those claims. Applicants would like to point out that claims 5-6, 8, 11, 14, 54, and 57 have been amended to be consistent with U.S. practice by removing the preferable ranges. Applicants therefore respectfully submit that the rejection under the second paragraph of 35 U.S.C. §112 has been obviated, and should be withdrawn.

The Examiner has rejected claim 12 as indefinite for the use of the term "about." This rejection is not well taken. Under U.S. law, the term "about" is considered to be "clear, but flexible." See MPEP § 2173.05(b) *citing Ex Parte Eastwood*, 163 U.S.P.Q. 316 (Bd. App. 1968). The term "about" does not render claim 12 indefinite, but rather merely adds permissible flexibility to the range provided in the claim. *Id.* Nonetheless, in order to further clarify the claim, Applicants have amended claim 12 to recite "an area of about 600 to about 900 $Å^2$." Applicants therefore respectfully submit that the rejection under the second paragraph of 35 U.S.C. § 112 has been obviated, and should be withdrawn.

The Examiner has rejected claims 25, 28, and 30-32 as unclear and therefore indefinite due to the absence of SEQ ID NO references in those claims. The Examiner asserts that, as written, the mutations are drawn to any residue on any amino acid sequence. Applicants would like to draw the Examiner's attention to the fact that claims 25 and 28 depend from claim 24. Accordingly, claims 25 and 28 are directed to mutations in Mal d 1, as recited in claim 24. Similarly, claims 30-32 depend from claim 29, and are directed to mutations in Dau c 1. Mal d 1 and Dau c 1 are well known in the art, as demonstrated by the Accession numbers provided in the specification. See page 29, lines 25-34 and page 32, lines 6-17. A person of ordinary skill in the art would understand that any of the identified proteins would be suitable scaffold proteins, and that the identified mutations in claims 25, 28, and 30-32 may be applied to result in a protein variant. Because both Mal d 1 and Dau c 1 are well known in the art and are adequately described in the

specification, specific sequence information is not necessary, and the mutations recited in claims 25, 28, and 30-32 are therefore definite.

The Examiner argues that claims 25 and 26 are unclear and therefore indefinite because the mutation Q76H is recited in both claims. Applicants respectfully submit that the Examiner is mistaken, and that claims 25 and 26 are proper Markush group claims. However, Applicants would like to point out that claim 26 has been amended, as discussed below, to delete reference to the specific mutations. Applicants respectfully submit that the amended claims are fully definite.

The Examiner also argues that claims 26 and 27 are indefinite because it is unclear whether the claimed protein variant constitutes the identified SEQ ID NOs, or whether the protein variant is the sequence after the mutations are introduced. Applicants respectfully note that claims 26 and 27 have been amended to remove reference to the specific mutations which are already included in the recited amino acid sequence.

For all the foregoing reasons, Applicants respectfully submit that the rejections for indefiniteness under 35 U.S.C. § 112, paragraph 2, have been fully obviated and should be withdrawn.

The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Examiner has rejected claims 1, 5-6, 9-10, 20-22, 55-56, and 59 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,583,046 to Valenta *et al.* ("Valenta"). Claims 1, 5-6, 8-9, 15, 20-24, and 52 have also been rejected under 35 U.S.C. § 102(b) as anticipated by Son *et al.*, Eur. J. Nutr., 1999, 38:201-215 ("Son"). In addition, the Examiner has rejected claims 54 and 73 under 35 U.S.C. § 102(b) as anticipated by the publication of King *et al.*, J. Immun., 2001, 166(10):6057-6065 ("King").

A. The Legal Standard of Anticipation

Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See M.P.E.P. §2131 (8th Ed. Rev. 2, May 2004). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must literally present, arranged as in the claim. *Perkin Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984).

B. Valenta Does Not Anticipate the Pending Claims

However, Valenta does not teach the use of a scaffold protein to maintain the three-dimensional folding pattern of the allergen, nor does Valenta teach the insertion of mutations in the scaffold protein as recited in claim 1. At best, Valenta teaches only proteins with amino acid homology. He does not teach proteins with structural similarity, *i.e.*, proteins with a similar tertiary structure. See Valenta, col. 3, line 56 to col. 4, line 9. Furthermore, the polypeptides of Valenta have the same or similar antigenicity as the native allergen, *i.e.*, their binding affinity to IgE antibodies specific for the native allergen is the same or similar. See col. 3, lines 17-30. The present invention, on the other hand, claims an increased or decreased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring antigen. See, for example, page 28, lines 10-21. Accordingly, Valenta does not teach all of the elements of the rejected claims, because it does not teach increased or decreased binding to IgE, and therefore does not anticipate the present application. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) under Valenta be withdrawn.

C. Son Does Not Anticipate the Pending Claims

The Examiner argues that Son teaches recombinant protein variants derived from apple strains and Bet v 1 clones. Applicants respectfully submit that Son does not teach all of the elements of the present invention. Son merely teaches, at best, the use of native allergens in which

point mutations are inserted. See pages 202, 204-205. In contrast, the present invention teaches the use of a scaffold protein which maintains the three-dimensional folding pattern of the allergen, and the introduction of point mutations into the scaffold protein, not into the allergen itself. See page 11, lines 15-27. In further contrast to the present invention, although Son teaches that point mutations inserted into the native allergen can cause a reduction in IgE binding capacity (see page 208), Son does not teach that mutations inserted into a scaffold protein would increase or decrease the binding affinity of IgE specific to the native allergen. See page 24, line 26 to page 25, line 16. Lastly, as noted in the present specification, modification of a naturally occurring allergen to reduce IgE binding affinity as disclosed in Son is not a desirable approach. See page 11, lines 7-13. Insertion of point mutations according to the method of Son creates a risk of destabilizing the three-dimensional structure of the molecule. *Id.* Indeed, Son does not address the possibility of disruption of the protein folding caused by the introduction of point mutations. In contrast, the present invention is directed to the introduction of mutations that preserve the three dimensional structure of the protein. See page 11, lines 15-27. Accordingly, Son does not teach all of the elements of the rejected claims, and therefore does not anticipate the present application. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) under Son be withdrawn.

D. King Does Not Anticipate the Pending Claims

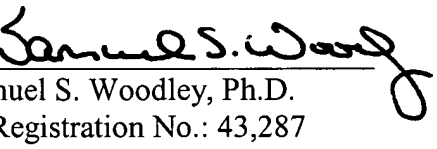
The Examiner argues that King teaches modified recombinant allergens consisting of a "host protein" which is used as a scaffold protein, which is fused with a "guest allergen." Applicants would like to point out that claim 54 has been amended to recite "comprises two or more primary mutations spaced by at least one non-mutated amino acid residue," as is recited in the other independent claims. Applicants note that King is directed to hybrid constructs wherein a scaffold protein is substituted with relatively long stretches of amino acids of a native allergen, and therefore does not contain "two or more primary mutations spaced by at least one non-mutated amino acid residue." As such, King does not teach all of the elements of the rejected claims, and therefore does not anticipate the present application. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) under King be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: February 24, 2005

Respectfully submitted,

By 

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